XP-002241668

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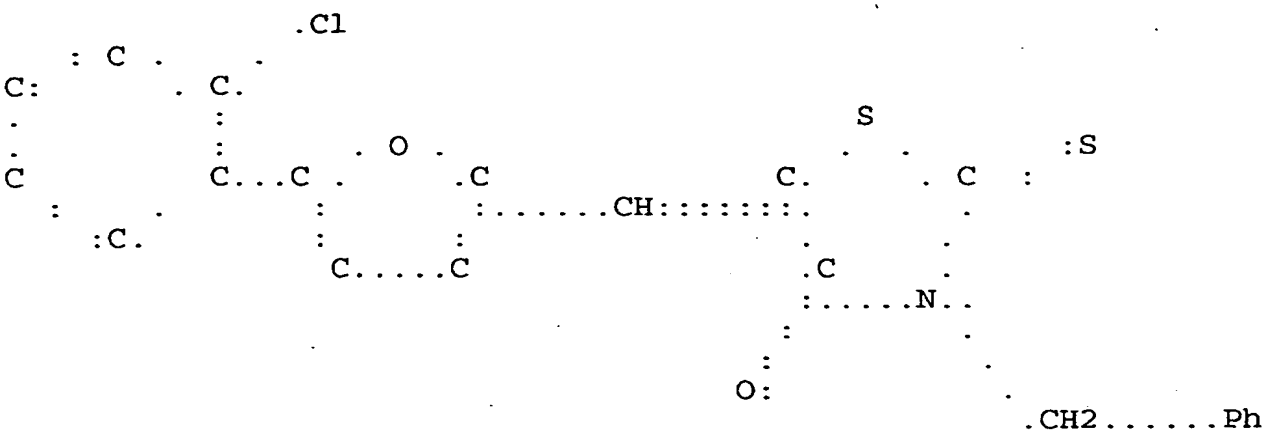
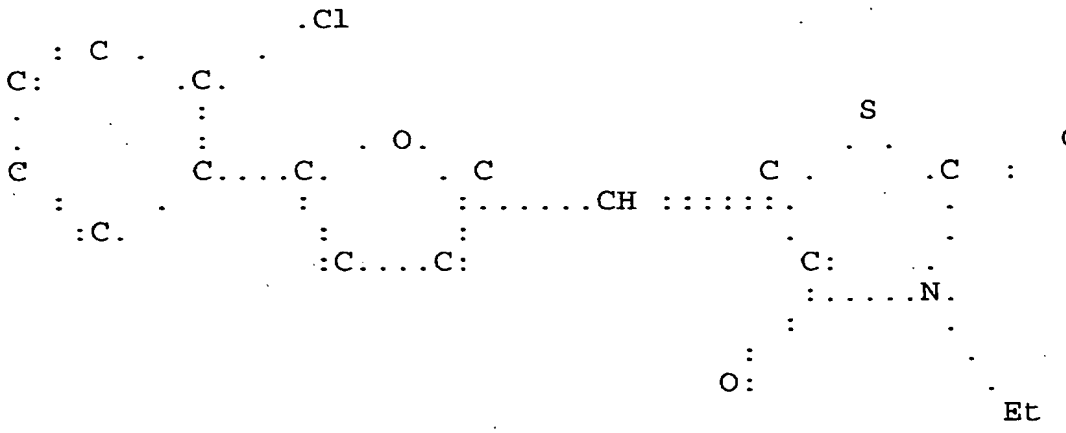
P. 1-5
S

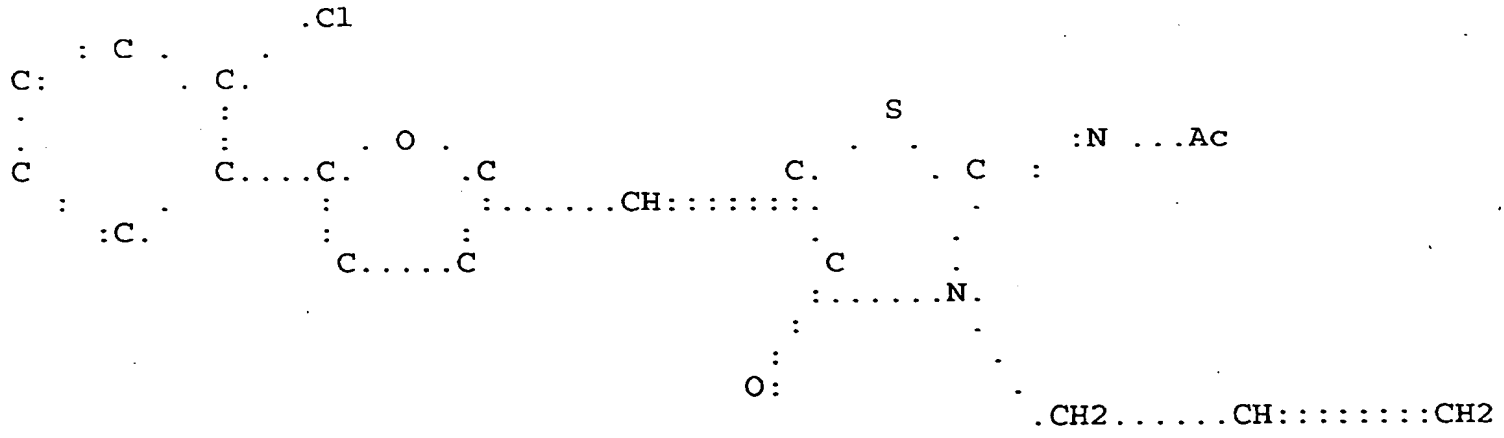
1/5 - (C) FILE CAPLUS
STN CA Caesar accession number : 1911
AN - 2001:763989 CAPLUS
DN - 136:95580
TI - Photochemically enhanced binding of small molecules to the tumor necro
factor receptor-1 inhibits the binding of TNF-.alpha.
IN - Carter, Percy H.; Scherle, Peggy A.; Muckelbauer, Jodi A.; Voss, Matth
E.; Liu, Rui-Qin; Thompson, Lorin A.; Tebben, Andrew J.; Solomon, Kimb
A.; Lo, Yvonne C.; Li, Zhong; Strzemienski, Paul; Yang, Gengjie;
Falahatpisheh, Nikoo; Xu, Meizhong; Wu, Zhongren; Farrow, Neil A.;
Ramnarayan, Kal; Wang, Jing; Rideout, Darryl; Yalamoori,
Venkatachalapathi; Domaille, Peter; Underwood, Dennis J.; Trzaskos, Ja
M.; Friedman, Steven M.; Newton, Robert C.; Decicco, Carl P.
CS - Experimental Station, DuPont Pharmaceuticals Company, Wilmington, DE,
19880-0500, USA
SO - Proceedings of the National Academy of Sciences of the United States o
America (2001), 98(21), 11879-11884
CODEN: PNASA6; ISSN: 0027-8424
PB - National Academy of Sciences
DT - Journal
LA - English
AB - The binding of tumor necrosis factor alpha (TNF-.alpha.) to the type-1
receptor (TNFRc1) plays an important role in inflammation .
Despite the clin. success to biologics (antibodies, sol. receptors) fc
treating TNF-based autoimmune conditions, no potent small mol. antagor
have been developed. Our screening of chem. libraries revealed that
N-alkyl 5-arylidene-2-thioxo-1,3-thiazolidin-4-ones were antagonists c
this protein-protein interaction. After chem. optimization, we discov
IW927, which potently disrupted the binding of TNF-.alpha. to TNFRc1
.apprxeq. 50 nM) and also blocked TNF-stimulated phosphorylation of
I.kappa.-B in Ramos cells (IC50 = 600 nM). This compd. did not bind
detectably to the related cytokine receptors TNFRc2 or CD40, and did r
display any cytotoxicity at concns. as high as 100 .mu.M. Detailed
evaluation of this and related mols. revealed that compds. in this cl
are "photochem. enhanced" inhibitors, in that they bind reversibly to
TNFRc1 with weak affinity (.apprx.40-100 .mu.M) and then covalently m
the receptor via a photochem. reaction. We obtained a crystal struct
of IV703 (a close analog of IW927) bound to the TNFRc1. This structu
clearly revealed that one of the arom. rings of the inhibitor was
covalently linked to the receptor through the main-chain nitrogen of
Ala-62, a residue that has already been implicated in the binding of
TNF-.alpha. to the TNFRc1. When combined with the fact that our
inhibitors are reversible binders in light-excluded conditions, the
results of the crystallog. provide the basis for the rational design
nonphotoreactive inhibitors of the TNF-.alpha.-TNFRc1 interaction.
IT - 389122-24-1 389122-25-2 389122-26-3
389122-27-4 389122-28-5 389122-29-6
389122-30-9 389122-31-0 389122-32-1
389122-33-2 389142-47-6 , IV 563
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); P
(Properties); THU (Therapeutic use); BIOL (Biological study); USES (U
(photochem. enhanced binding of N-alkyl 5-arylidene-2-thioxo-1,3-
thiazolidin-4-ones to tumor necrosis factor receptor-1 inhibits bin
of TNF-.alpha.)
RN - 389122-24-1 CAPLUS
CN - 4-Thiazolidinone, 5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-2-thiox
(5Z)- (9CI) (CA INDEX NAME)



STEREO DIAGRAM AVAILABLE WITH GRAPHICS TERMINAL OR OFFLINE PRINT
RN 389122-28-5 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-3-eth
, (5Z)- (9CI) (CA INDEX NAME)



STEREO DIAGRAM AVAILABLE WITH GRAPHICS TERMINAL OR OFFLINE PRINT
RN 389122-29-6 CAPLUS
CN Acetamide, N-[(5Z)-5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-4-oxo-3-(
propenyl)-2-thiazolidinylidene]- (9CI) (CA INDEX NAME)



STEREO DIAGRAM AVAILABLE WITH GRAPHICS TERMINAL OR OFFLINE PRINT

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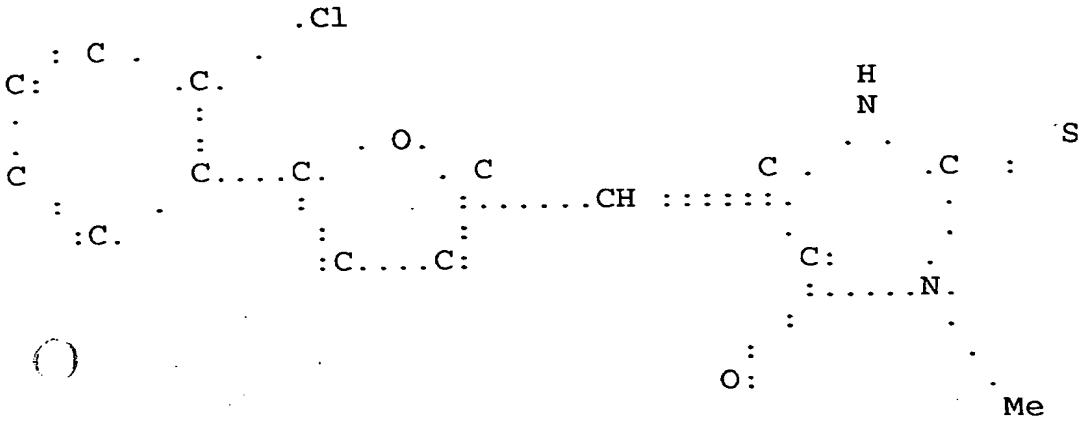
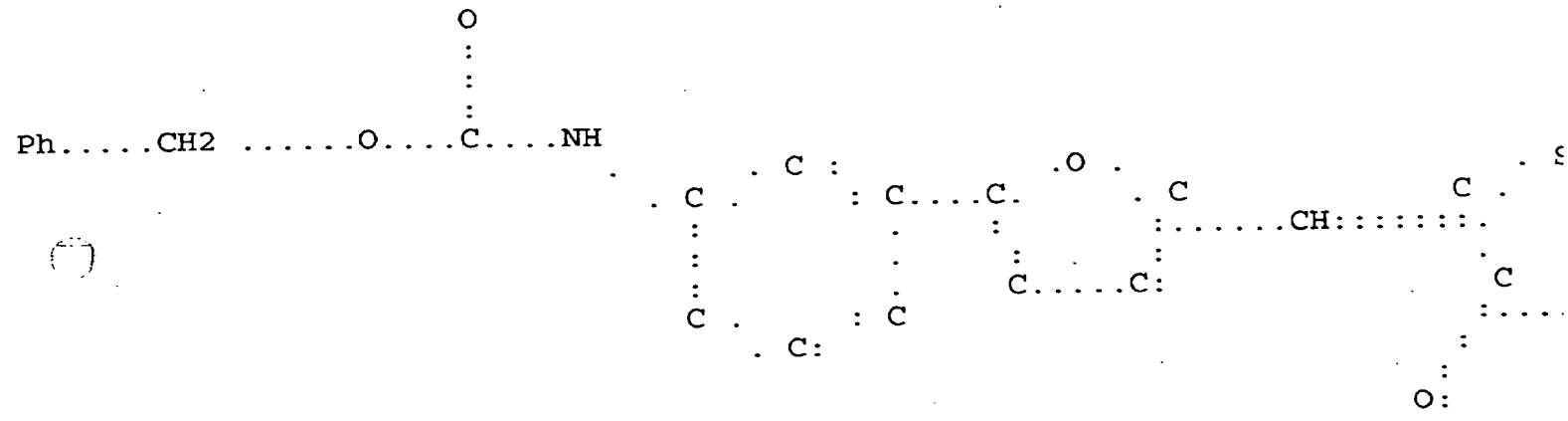
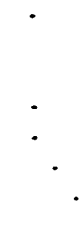
STEREO DIAGRAM AVAILABLE WITH GRAPHICS TERMINAL OR OFFLINE PRINT
RN 389122-33-2 CAPLUS
CN 4-Imidazolidinone, 5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-3-methyl-2-thioxo-, (5Z)- (9CI) (CA INDEX NAME)



STEREO DIAGRAM AVAILABLE WITH GRAPHICS TERMINAL OR OFFLINE PRINT
RN 389142-47-6 CAPLUS
CN Carbamic acid, [3-[5-[(Z)-(3-ethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-furanyl]phenyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



Page 1-A



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Page 1-B
STEREO DIAGRAM AVAILABLE WITH GRAPHICS TERMINAL OR OFFLINE PRINT
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD